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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DUBINI, Adriana [IT/IT]; Via San Giacomo Moro, 16, I-20100 Milano (IT). McCALL, John, Michael [US/US]; 1128 North Eagle Lake Drive, Kalamazoo, MI 49009 (US). TAYLOR, Duncan, Paul [US/US]; 8722 West F Avenue, Kalamazoo, MI 49009 (US). VON VOIGTLANDER, Philip, F. [US/US]; 1 South Lake Doster, Plainwell, MI 49080 (US). WONG, Erik, Ho, Fong [US/US]; 7352 Hampstead Lane, Portage, MI 49024 (US).

(74) Agent: WOOTTON, Thomas, A.; Pharmacia & Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

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Published

Without international search report and to be republished upon receipt of that report.

(54) Title: NEW TREATMENTS FOR NERVOUS DISORDERS

(57) Abstract

This patent application describes the treatment of Obsessive Compulsive Disorders (OCD), and Panic Disorder (PD), comprising administering a therapeutically effective, nontoxic dose of reboxetine and derivatives and/or pharmaceutically acceptable salts thereof to a patient.

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NEW TREATMENTS FOR NERVOUS DISORDERS

Field of the Invention

This invention describes new treatments for several nervous system disorders, including: Obsessive Compulsive Disorders, and Panic Disorder. The treatment involves the administration of the drug reboxetine.

Background

The introduction of tricyclic antidepressants in the early 1960s has provided a major advance in the treatment of neuropsychiatric disorders. Reactive and endogenous depressions, diagnoses formerly carrying grave prognostic implications, have become, with the introduction of the tricyclics, manageable disorders with a much smaller toll on the patient and the society as a whole.

The early tricyclic compounds were reuptake inhibitors of all the catecholamines released in the synaptic cleft, thus resulting in prolongation and enhancement of the dopamine (DA), noradrenaline (NA) and serotonin (5-hydroxytryptamine = 5-HT) action. Lack of selectivity also causes undesired side effects particularly on the acetylcholine (especially the muscarinic component), and histamine mediated neurotransmission.

Because of these unwanted pharmacodynamic activities, cognitive impairment, sedation, urinary and gastrointestinal tract disturbances, increased intraocular pressure were limiting factors in the clinical use of these compounds and often required discontinuation of treatment. Of utmost concern were also the cardiac toxic effects and the proconvulsant activity of this group of drugs.

More recently, selective reuptake inhibitors for serotonin (SSRI) have been introduced with definite advantages in regard to fewer side effects without loss of efficacy.

Here we present the surprising finding that one particular drug from a new category of antidepressants, a so called noradrenaline (NA) reuptake inhibitor can be used to manage or treat a few special diseases, diseases having symptoms outside of what are usually considered depression symptoms.

Summary of the Invention

This patent application describes the treatment of Obsessive Compulsive Disorders (OCD), and Panic Disorder (PD), comprising administering a therapeutically effective,

nontoxic dose of reboxetine and derivatives and or pharmaceutically acceptable salts thereof to a patient.

Reboxetine is the generic name of the pharmaceutical substance with the chemical name of 2-(1-((2-ethoxyphenoxy)benzyl)-morpholine, and its pharmaceutically acceptable salts. Reboxetine can be a free base, or it can include reboxetine methanesulfonate (also called reboxetine mesylate) or any other pharmaceutically acceptable salt that does not significantly affect the pharmaceutical activity of the substance.

A preferred dose range is 4 to 10 mg per patient per day and the most preferred dose is 6 to 8 mg or 8 to 10 mg per patient daily, depending upon the patient, delivered twice a day (b.i.d.).

Additional Description of the Invention and Description of the Preferred Embodiment(s)

Reboxetine is the generic name of the pharmaceutical substance with the chemical name of 2-(1-((2-ethoxyphenoxy)benzyl)-morpholine, and its pharmaceutically acceptable salts. Reboxetine can be a free base, or it can include reboxetine methanesulfonate (also called reboxetine mesylate) or any other pharmaceutically acceptable salt that does not significantly affect the pharmaceutical activity of the substance. Reboxetine and a method of synthesis are described in U.S. 4,229,449, issued 21 Oct. 1980, Melloni *et. al.*, incorporated by reference, methods of preparation are described in US 5,068,433, issued 26 Nov. 1991, Melloni *et. al.* and in US 5,391,735, issued 21 Feb. 1995, both incorporated by reference. Reboxetine may also be known under the trade name of EDRONAX™.

The pharmaceutical compositions and methods of administration described in US 4,229,449 at col. 18, lines 33-66 are specifically incorporated by reference. Twice a day dosing is preferred with current formulations.

Reboxetine acts as an antidepressant. Antidepressants are frequently grouped into categories or "generations." The first generation of antidepressants were usually tricyclic antidepressants such as maprotiline that affected various neurotransmitter systems and are associated with many undesirable side effects. The second generation of antidepressants, such as mianserine, mirtrazapine and trazodone are largely devoid of anticholinergic action and their adrenolytic and antihistaminic effects are weaker. These are contrasted with the third generation of antidepressants (e.g. SSRI, ipsapirone, viloxazine, reboxetine, bupropione) that mediate only one of the three main neurotransmitter system for

depression (5-HT, noradrenaline, dopamine) and they do not affect muscarine, histamine and adrenergic cerebral systems. Svestka, J. "Antidepressives of the 3rd, 4th and 5th generation," *Cesk-Psychiatr.* 1994 Feb; 90(1):3-19. (Czech).

Reboxetine, however, does not act like most antidepressants. Unlike tricyclic antidepressants and even selective serotonin reuptake inhibitors (SSRIs), reboxetine is ineffective in the 8-OH-DPAT hypothermia test, indicating that reboxetine is not a selective serotonin reuptake inhibitor, instead it is selective for the noradrenergic system. Thus, reboxetine is not an SSRI, rather it is considered a novel, selective, noradrenaline-reuptake inhibitor (NARI). Leonard-BE, "Noradrenaline in basic models of depression." *European-Neuropsychopharmacol.* 1997 Apr; 7 Suppl 1: S11-6; discussion S71-3. Unlike most drugs, reboxetine is a highly selective norepinephrine uptake inhibitor, with only marginal serotonin and no dopamine uptake inhibitory activity. The compound displays only weak or no anti-cholinergic activity in different animal models and is devoid of monoamine oxidase (MAO) inhibitory activity.

Reboxetine is highly potent and fast acting. Our investigations indicate reboxetine has potent antireserpine activity and combines the inhibitory properties of classical tricyclic antidepressants on the reuptake of noradrenaline with an ability to desensitize β-adrenergic receptor function without showing any appreciable interaction with muscarinic cholinergic and I-adrenerigic receptors. Moreover, reboxetine shows less vagolytic activity than other tricyclic antidepressants.

The inventors have discovered that, in addition to its unique properties, mentioned above, reboxetine has been found particularly useful for treating or enhancing the treatment of a few psychiatric symptoms or disorders, with greater efficacy and with fewer side effects, than with treatment by known drugs. Furthermore, the inventors here have discovered that reboxetine can also be used to treat, or to enhance the treatment, of a few other specific psychiatric symptoms or disorders. The new symptoms or disorders amenable to treatment with reboxetine are provided below.

The dosage used to treat all of the disorders described here is as follows. Reboxetine is well tolerated and has a wide safety range, it can be administered in a dose range of active ingredient from about 1 to over 20 mg/kg. It is more commonly provided in dosages of from 1 to 20 mg per patient per day. The compound may be administered by any suitable method including a convenient oral dosage form. A preferred method is oral dosing twice a day. The preferred dose range is 4 to 10 mg per patient per day and

the most preferred dose is 6 to 8 mg or 8 to 10 mg per patient daily, depending upon the patient, delivered twice a day (b.i.d.). It can also be given at dosages of 2, 4, 6, 8, 10 or 12 mg/patient per day or fractions thereof: For example, suitable administrations could be 4 mg in the morning and 2 or 4 mg in the evening. In some patients the ideal dosing would be 3-5 mg in the morning and 3-5 mg in the evening. A skilled practitioner would be expected to determine the precise level of dosing. The idea dosing would be routinely determined by an evaluation of clinical trials and the needs of the patient.

The diseases described for treatment here are:

I. Obsessive Compulsive Disorders (OCD)

Obsessive Compulsive Disorder is a condition or state of anxiety that may be treated with reboxetine. General descriptions of OCD, may be found in many standard sources, such as, The American Psychiatric Press Textbook of Psychiatry, Second Edition, Edited by Robert E. Hales, Stuart C. Yudofsky, and John A. Talbott, copyright 1994, incorporated by reference, especially the chapter on "Anxiety Disorders," incorporated by reference. Another of many texts is the Manual of Psychiatric Therapeutics, Second Edition, edited by Richard I. Shader, incorporated by reference, especially Chapter 5, Obsessions and Compulsions, more particularly, Section III of that chapter, "OCD" pp. 36 *et. seq.*, incorporated by reference.

The treatment of Obsessive Compulsive Disorders (OCD) involves the administration of reboxetine in a manner and form that provide a reduction in the symptoms of the disease. See general description above for administration of reboxetine.

The following study shows the therapeutic effectiveness of using reboxetine in doses varying from 6 to 8 mg to treat OCD. This study is provided to illustrate the usefulness of using reboxetine as a treatment for OCD and the invention described herein should not be considered limited by this example.

In a trial involving 10 patients with a DSM-III-R diagnosis of Obsessive Compulsive Disorder who were all treated with reboxetine for a period of 3 to 4 weeks with the dose for the first week at 6 mg (4 mg in a.m. and 2 mg in p.m.) with the dose increasing in the second week to 8 mg (4 mg b.i.d.). At CGI last assessment, one patient was judged very much improved, 4 were judged much improved, 2 minimally improved, while 3 were unchanged. Of the patients who did respond they had a decrease of the obsessive-compulsive symptomatology, as measured by the CPRS-OC rating scale, of more than 30 and as much as 73%.

II. Panic Disorder (PD).

Panic Disorder is a condition or state of anxiety that may be treated with reboxetine. General descriptions of PD, may be found in many standard sources, such as, The American Psychiatric Press Textbook of Psychiatry, Second Edition, Edited by Robert E. Hales, Stuart C. Yudofsky, and John A. Talbott, copyright 1994, incorporated by reference, especially the chapter on "Anxiety Disorders," incorporated by reference, another of many texts is the Manual of Psychiatric Therapeutics, Second Edition, edited by Richard I. Shader, incorporated by reference, especially Chapter 25, "Approaches to the Treatment of Anxiety States," incorporated by reference.

The treatment of Panic Disorder involves the administration of reboxetine in a manner and form that provide a reduction in the symptoms of the disease. See general description above for administration of reboxetine.

The following study shows the therapeutic effectiveness of using reboxetine in doses varying from 6 to 8 mg to treat Panic Disorder. This study is provided to illustrate the usefulness of using reboxetine as a treatment for PD and the invention described herein should not be considered limited by this example.

In a trial involving 75 patients that satisfied the DSM-III criteria for the diagnosis of Panic Disorder with or without Agoraphobia (300.01, 300.21) and had at least 4 panic attacks in the month preceding their admission, in a randomized, placebo controlled parallel group, double blind design, 37 on reboxetine and 38 on placebo, the mean number of major panic attacks for patients treated with reboxetine was significantly lower than for those on placebo. Phobic symptoms, anticipatory anxiety, occupational functioning, social and family adjustment were all better at some point in time for those treated with reboxetine than for patients on placebo.

Claims

1. A method of treating or enhancing the treatment of a disorder selected from:

a) Obsessive Compulsive Disorders (OCD); and/or

b) Panic Disorder (PD);

comprising administering a therapeutically effective, nontoxic dose of reboxetine and derivatives and or pharmaceutically acceptable salts thereof to a patient experiencing the symptoms of those disorders.

2. The method of claim 1 where reboxetine is used to treat or enhance the treatment of Obsessive Compulsive Disorders (OCD).

3. The method of claim 1 where reboxetine is used to treat or enhance the treatment of Panic Disorder (PD).

4. The preparation of a medicament to treat OCD or PD from a composition comprising reboxetine.

5. The use of reboxetine or its pharmaceutically acceptable salts in the manufacture of a medicament to treat Obsessive Compulsive Disorders (OCD); and/or Panic Disorder (PD);

and/or for the treatment of any of the symptoms of either of those diseases.

6. The method or use in claims 1-5 where the reboxetine dose range is 4 to 10 mg. per patient per day.

7. The method or use in claims 1-5 where the reboxetine dose range is 6 to 8 mg. per patient per day.

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A3

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Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

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(54) Title: NEW TREATMENTS FOR NERVOUS DISORDERS

(57) Abstract

This patent application describes the treatment of Obsessive Compulsive Disorders (OCD), and Panic Disorder (PD), comprising administering a therapeutically effective, nontoxic dose of reboxetine and derivatives and/or pharmaceutically acceptable salts thereof to a patient.

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INTERNATIONAL SEARCH REPORT

Inter tional Application No
PC1/US 99/04288

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	B.E.LEONARD: "Noradrenaline in basic models of depression" EUR.NEUROPSYCHOPHARMACOL., vol. 7, no. suppl. 1, 1997, pages S11-S16, XP002113301 the whole document page S11, right-hand column ---	1-7
E	WO 99 20279 A (ELI LILLY AND COMPANY) 29 April 1999 (1999-04-29) page 3, line 26 page 5, line 21 - page 6, line 13 page 9, line 27 claim 5 --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
25 August 1999	13/10/1999

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	W.J.KATON: "Depression and Anxiety: New Tools for Diagnosis and Treatment" J. CLIN.PSYCHIATRY, vol. 59, no. Suppl. 20, 1998, pages 3-4, XP002113302 See footnote on page 3 the whole document	1-7
X	A.F.SCHATZBERG: "Noradrenergic Versus Serotonergic Antidepressants: Predictors of Treatment Response" J.CLIN.PSYCHIATRY, vol. 59, no. Suppl. 14, 1998, pages 15-18, XP002113303 See footnote on page 15 the whole document	1-7
X	S.A.MONTGOMERY: "The Place of Reboxetine in Antidepressant Therapy" J.CLIN.PSYCHIATRY, vol. 59, no. Suppl. 14, 1998, pages 26-29, XP002113304 See footnote on page 26 the whole document	1-7
X	A.DUBINI ET AL.: "Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning" J.PSYCHOPHARMACOL., vol. 11, no. 4 Suppl., 1997, pages S17-S23, XP002113305 the whole document	1-7
X	M. MUCCI: "Reboxetine: a review of antidepressant tolerability" J.PSYCHOPHARMACOL., vol. 11, no. 4 Suppl., 1997, pages S33-S37, XP002113306 the whole document	1-7
X	H.BERZEWSKI ET AL.: "Efficacy and tolerability of reboxetine compared with imipramine in a double-blind study oin patients suffering from major depressive episodes" EUR.NEUROPSYCHOPHARMACOL., vol. 7, no. Suppl. 1, 1997, pages S37-S47, XP002113307 the whole document	1-7

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/04288

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. DUBINI ET AL.: "Do noradrenaline and serotonin differentially affect social motivation and behaviour?" EUR. NEUROPSYCHOPHARMACOL., vol. 7, no. Suppl. 1, 1997, pages S49-S55, XP002113308 the whole document	1-7
X	"Discussion" EUR. NEUROPSYCHOPHARMACOL., vol. 7, no. Suppl. 1, 1997, pages S71-S73, XP002113309 the whole document	1-7
X	J.F.W.DEAKIN: "Does selectivity matter?" INT.CLIN.PSYCHOPHARMACOL., vol. 11, no. Suppl. 1, 1996, pages 13-17, XP002113310 abstract	1-7
A	DE 35 40 093 A (FARMITALIA CARLO ERBA S.P.A.) 28 May 1986 (1986-05-28) page 22, line 31 - page 23, line 13	1-7
A	DE 29 01 032 A (FARMITALIA CARLO ERBA S.P.A.) 2 August 1979 (1979-08-02) page 34, line 1 - line 4	1-7

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 99/04288

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-3 and 6-7
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-3 and 6-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/04288

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9920279 A	29-04-1999	AU 9692898 A	10-05-1999
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